REMARKS

Applicant hereby acknowledges the election to Group I (claims 1-31). Applicant also acknowledges renumbering of claim 27 as claim 71. The claims currently under consideration in the case are claims 1-31 and 71.

Applicants acknowledge, with appreciation, that the Examiner has considered four references that were submitted, but not listed on the form 1449. Applicants thank the Examiner for including a Form 892 to make these references of record.

The following informalities have been corrected:

(a) Sequence identifiers are provided for original pages 19, 20, and 37-47.

(b) Extraneous parenthetical phrases have been removed from original pages 18 and 25.

(c) Table I has been reformatted with respect to the column labeled "AMP^R colonies".

Applicants respectfully submit that the Specification is in compliance with the requirements of 37 CFR 1.821 through 1.825, and is otherwise in good form.

Claim objections

The claims in the case are claims 19-36. Applicants acknowledge, with appreciation, the withdrawal of the rejection of the claims under 35 U.S.C. §112, first paragraph.

The claims have been amended such that claim 71 now is properly drawn to the method of claim 3, and claim 26 is drawn to bacteria that express a protein that consists

of the first 133 amino acids of PMS2. The comma has been removed after the word "hypermutable" in claim 18, and claims 30 and 31 now consistently use the spelling "eukaryotic". Applicants earnestly submit that the claims are in proper form for allowance.

Furthermore, claim 26 has been amended to correct the typographical error "thebacteria" to "the bacteria". Claim 1 has been amended to recite "said bacterium" rather than "cell," which lacked antecedent basis. Finally, for simplicity, claims 2-5 have been amended to simply recite that the mismatch repair gene encodes a MutS, MutL, MutH, or MutY protein. The amendment is not intended to change the scope of the claim as filed.

Claim Rejections – 35 U.S.C. §112

1. Written Description

The Office Action rejects claims 1-16, 18-25 and 28-31 under the "Written Description" Requirement. The Office Action alleges that claim 1 is drawn to a method of making a hypermutable bacterium comprising introducing a dominant negative allele of a mismatch repair gene into the bacterium. The Office Action further alleges that only one type of dominant negative allele is disclosed in the specification, and that overexpression of mismatch repair alleles to produce a dominant negative effect, is not the same as a dominant negative allele. The Examiner correctly points out that overexpression of eukaryotic mismatch repair genes in bacteria to cause an inhibition of mismatch repair is more accurately referred to as a "dominant negative effect" rather than a dominant negative allele, such as the PMS2-134 allele. The Specification also uses this

terminology at page 11, lines 17-21, wherein it is stated "Expression of a dominant negative allele of a mismatch repair gene results in an impairment of mismatch repair activity, even in the presence of the wild-type allele. Any mismatch repair allele, which produces such effect, can be used in this invention." Therefore, the claims have been amended to point out more particularly and to claim more distinctly the invention by using the term "form of a mismatch repair protein." The subject matter is fully supported in the Specification, the claims now read more precisely, using the terminology of those of skill in the art.

The Examiner also correctly points out that other dominant negative forms of mismatch repair proteins were known for bacteria (*e.g.*, MutL and MutS). The Application as filed clearly contemplates the use of polynucleotides encoding these forms of mismatch repair proteins along with eukaryotic dominant negative alleles (*e.g.*, *PMS2-134*) as well as the overexpression of wild-type eukaryotic mismatch repair genes.

The claims, as amended, are descriptive of a representative number of species encompassed by the claims. The claims, which are drawn to polynucleotides encoding mismatch repair proteins that exert a dominant negative effect now encompass truncation mutations disclosed by the specification and as known in the art for MutS and MutL, as well as overexpression of eukaryotic mismatch repair proteins, which exerts a dominant negative effect on bacterial mismatch repair. The Applicants were clearly in possession of these representative embodiments of the invention at the time of filing, and the Specification provides guidance as to (1) the definition of the dominant negative effect on mismatch repair as well as (2) methods for identifying dominant negative alleles (see Specification at page 11, lines 25-30 through page 12, lines 1-15 and citing Nicolaides *et*

al. (1998) *Mol. Cell. Biol.* 18:1635-1641) and (3) assays for the dominant negative effect (see Specification at page 12, lines 16-20, and citing Nicolaides *et al.* (1998) *Mol. Cell. Biol.* 18:1635-1641) and hypermutability (see Specification Example 2). Applicants earnestly submit that the Written Description Requirement is fulfilled.

2. Enablement

The Office Action also rejects claims 1-16, 18-25, and 28-31 under 35 U.S.C. §112, first paragraph, as enabling only for truncation mutants of human PMS2, and *E. coli* MutS and MutL.

The Office Action alleges that the Specification does not provide sufficient enablement for use of other genes and that the specification, therefore, does not provide enablement commensurate with the scope of the claims. Applicants respectfully disagree.

(a) Truncation Mutants

The Specification describes the use of human PMS2-134, a truncation mutant that confers a dominant negative effect on mismatch repair. The Examiner agrees that this is enabled by the Specification. However, the Specification also discloses the use of a PMS2 homolog in the plant *Arabidopsis thaliana* which was designed with a similar truncation after the 133 amino acid of the *A. thaliana* PMS2 (AtPMS134). The Specification demonstrates, in an example (Example 2) that the AtPMS134 homolog exerted a similar dominant negative effect in bacteria (See Figure 5). Furthermore, the literature describes dominant negative alleles of *mutS* and *mutL* which may be used in the method of the invention. Both the literature and the Specification describe methods for

identifying dominant negative alleles of mismatch repair genes. Thus, the Specification provides a representative number of examples of truncation mutants, expressly and by reference, that may be used within the scope of the invention. Moreover, the Specification provides working examples of human and plant truncation mutants of PMS2 that exert a dominant negative effect.

(b) Bacterial Homologs

Mismatch repair is a highly conserved process found in prokaryotic and eukaryotic organisms. MutS and MutL proteins involved in bacterial mismatch repair and dominant negative mutants have been described in the literature for *E. coli*, as referenced in the Specification and as noted by the Examiner. Thus, the Specification provides sufficient information, expressly, and by reference, that dominant negative forms of MutS and MutL could be used in the method of the invention. MutL and MutS are known for many different genera and species of bacteria, and this would be known to one of ordinary skill in the art. It is not a requirement for the Specification to list each and every sequence or citation for the MutS and MutL homologs. These would be known to one of ordinary skill in the art. The Specification does, however, provide the necessary guidance to determine dominant negative alleles for mismatch repair genes and assays for function of such genes, such that one could practice the invention without undue experimentation. It must be remembered that even a significant amount of experimentation is permitted in an enabling disclosure, so long as it is not undue. Of particular relevance is the fact that the specification provides guidance as to the genes that may be employed, that homologs may be used, and provides specific assays to identify alleles that exert the dominant negative effect when expressed.

(c) Eukaryotic Overexpression

The Specification provides specific examples of alleles that produce a dominant negative effect in Example 3 in which mutant bacteria were tested for acquiring heat resistance. PMS-134 mutants and PMSR3 mutants showed acquisition of heat resistance for several colonies of bacteria (see Table 2). Furthermore, the Specification states at page 28, lines 8-10, "Similar results were observed with other dominant negative mutants such as the PMSR2, PMSR3 and the human MLH1 proteins (not shown)."

Thus, the Specification provides evidence of enablement for use of mismatch repair genes beyond human PMS-134 and *E. coli* MutL and MutS. Applicants respectfully submit that the Specification is commensurate with the scope of the claims, as amended.

35 U.S.C. §102(b)

The Office Action rejects claims 1, 4, 13, 18, and 29 under 35 U.S.C. §102(b) over Aronshtam *et al.* (1996) *Nucl. Acids Res.* 24:2498-2504 ("Aronshtam") alleging that Aronshtam teaches transformation of bacteria with a plasmid expressing a dominant negative allele of *Escherichia coli mutL* (plasmid pMQ393) under the control of an inducible promoter (T7) with the *lac* operator (which is inducible by the addition of isopropylthiogalactoside (IPTG)).

Aronshtam's goal was to characterize MutL to identify functional domains of MutL by using a dominant negative mutational strategy (see Aronshtam, page 2498, Col. 2, last paragraph). Aronshtam induced some bacteria with IPTG for purification of histidine-tagged MutL from cultures (see page 2500, "Purification of His-tagged MutL, antisera preparation and Western blotting"). According to Figure 1, and the Materials

and Methods for "Bacterial Strains and Plasmids," the His-tagged MutL gene is on plasmid pMQ378. This appears to be a wild-type MutL, rather than a dominant negative mutant. Further evidence of this is found at page 2500, last paragraph through the first paragraph on page 2501, wherein it is stated that the *mutL* gene, with the His-tagged coding region was subcloned from pMQ378 into vector pACYC184 to generate the derivative pMQ393 (which contains the T7 promoter). The pMQ393 was subsequently mutated using hydroxylamine, but Aronshtam does not state that pMQ393 was ever induced. In fact, Aronshtam states that λ DE3 derivatives of CC106 (shown in Table 2 as GM5861) were used for the complementation assays (see page 2499, column 2, under "Genetic complementation" wherein it is stated that "Each CC106 derivative" containing a plasmid conferring dominant negative *mutL* phenotype was transformed with a plasmid containing wild-type *mutL*, *mutH* or *mutS*). As described in the literature for Novagen pET plasmids, bacterial cells carrying λ DE3 produce their own T7 RNA polymerase. Such bacterial cells "allow some degree of transcription in the uninduced state and in the absence of further controls, are suitable for expression of many genes whose products have innocuous effects on host cell growth" (see Feature Article, page 2, column 2, a copy is enclosed for the Examiner's convenience). Thus, Aronshtam did not induce the cells to produce dominant negative proteins despite the use of an inducible promoter.

As the step of inducing the bacterial cells is not taught in Aronshtam, it does not anticipate the claims, as amended. Withdrawal of the rejection is respectfully solicited.

35 U.S.C. §103(a)

The Office Action rejects claims 1, 3, 18, and 23 under 35 U.S.C. §103(a) over Wu *et al.* (1994) *J. Bacteriol.* 176:5393-5400 ("Wu") in view of Winnacker, GENES TO CLONES, INTRODUCTION TO GENE TECHNOLOGY (translation by Horst Ibelgaufts), Weinheim, New York, VCH, 1987, pp. 241-242 ("Winnacker"). The Office Action alleges that Wu teaches bacteria transformed with a dominant negative allele of *Escherichia coli MutS* that results in hypermutability. The Examiner frankly admits that Wu does not teach an inducible promoter to control the expression of the dominant negative allele. The Office Action further alleges that it would be obvious for one of ordinary skill in the art to express the dominant negative alleles using an inducible promoter to avoid toxicity issues and overexpression of protein during cell division. The Office Action cites Winnacker to support this assertion. However, a careful consideration of the reference reveals that Winnacker is specifically referring to the expression of *foreign* proteins in bacterial cells. The reference does not teach that endogenous proteins of *E. coli*, (albeit mutant versions) such as *MutS* should be under the control of an inducible promoter. Moreover, Wu does not provide adequate incentive to express the mutant proteins under the control of an inducible promoter. The statement in Wu that purification of mutant proteins for use in biochemical assays might uncover the mechanistic basis of the results in Wu's study, does not teach, suggest, or imply that one should express such proteins under the control of an inducible promoter. That reasoning is pure speculation by the Patent Office and does not come from the teachings of Wu or Winnacker, alone or in the hypothetical combination proposed in the Office Action. In order to properly combine references under 35 U.S.C. §103(a), it is axiomatic that the references must provide an explicit or inherent motivation to combine the teachings, and

a reasonable expectation of success that the hypothetical combination would result in the claimed invention. It is improper for the Patent Office to impute motivation to prior art references using hindsight gained from the application. Further, while it may be obvious to try an inducible promoter, it is well-established that "obvious-to-try" is not an appropriate standard under 35 U.S.C. §103. Wu does not suggest that the mutant proteins are toxic, or that overexpression should be controlled; and Winnacker does not apply the reasoning regarding expression of foreign proteins to expression of mutant endogenous proteins. Thus, there is insufficient motivation to combine the teachings of the references in the references themselves. The Applicants respectfully request withdrawal of the rejection of the claims under 35 U.S.C. §103 over Wu in view of Winnacker.

The Office Action further rejects claims 1, 6, 7, 14, 15, 17, 18, 20, 24-27 and 71 under 35 U.S.C. §103(a) over U.S. Patent No. 6,146,894 to Nicolaides *et al.* ("Nicolaides") in view of Winnacker and Aronshtam. This rejection is respectfully traversed.

Nicolaides is cited for teaching making hypermutable mammalian cells by introducing a dominant negative allele of a mismatch repair gene. The Office Action states that Nicolaides does not teach an inducible promoter or using a bacterial cell. The Examiner alleges that it would have been obvious for one of ordinary skill in the art to express a dominant negative allele of PMS2 under the control of an inducible promoter in bacterial cells for the following reasons:

(a) to create, screen, and study protein mutants;

(b) for molecular manipulation and large-scale culturing; and

(c) to avoid toxicity during expression of foreign genes.

The claims require introducing the dominant negative allele under the control of an inducible promoter. Creating, screening and studying protein mutants can be done in eukaryotic systems as well as prokaryotic systems. Using bacterial cells has certain advantages for some applications, but the claims are drawn to making hypermutable bacterial cells, not simply use of bacterial cells to manipulate mismatch repair alleles. Creating, screening and studying of protein mutants (even in bacterial cells) does not require the use of an inducible promoter.

Likewise, molecular manipulation and large-scale culturing may be done in eukaryotic systems (*e.g.*, insect expression systems and mammalian cell systems) and does not require an inducible promoter. Winnacker teaches that expression of foreign genes in bacterial cells may be accompanied by toxicity, which may be avoided by the use of an inducible promoter, however, that is generally used for systems in which a foreign protein is to be produced in large quantities for purification. The claims are drawn to methods of making hypermutable bacteria, not methods of making large quantities of mutant mismatch repair proteins. The combination of Nicolaides and Winnacker for the purpose of making large quantities of mismatch repair proteins is disparate from the scope of the claims. Thus, there is insufficient motivation to combine the teachings of Nicolaides and Winnacker.

Double Patenting

As described above, the teachings of Nicolaides, Winnacker and Aronshtam do not render the pending claims obvious over the claims of U.S. Patent No. 6,146,894. Thus, there is no issue of double patenting under the judicially-created doctrine of

obviousness-type double patenting. Applicants respectfully request withdrawal of the double patenting rejection.

Applicants earnestly submit that the claims are in condition for allowance, which action is respectfully requested.

Respectfully submitted,

Date: October 16, 2002

By: _____
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Version with Markings to Show Changes Made

In the Claims

1. (Amended) A method for making hypermutable bacteria comprising the [step] steps of:

introducing into a bacterium a polynucleotide encoding a [comprising a dominant negative allele] form of a mismatch repair [gene] protein under the control of an inducible transcription regulatory sequence[,]; and

inducing said inducible transcription regulatory sequence in said bacterium; wherein said form of said mismatch repair polynucleotide exerts a dominant negative effect on mismatch repair when expressed in said bacterium, whereby [the cell] said bacterium becomes [inducibly] hypermutable.

2. (Amended) The method of claim 1 wherein the mismatch repair gene is MutH[from any species].

3. (Amended) The method of claim 1 wherein the mismatch repair gene is [a] MutS [homolog from any species].

4. (Amended) The method of claim 1 wherein the mismatch repair gene is MutL[homolog from any species].

5. (Amended) The method of claim 1 wherein the mismatch repair gene is [a] MutY [homolog from any species].

12. (Amended) The method of claim 3 wherein said [allele] polynucleotide encoding a form of a mismatch repair protein comprises a truncation mutation.

13. (Amended) The method of claim 4 wherein said [allele] polynucleotide encoding a form of a mismatch repair protein comprises a truncation mutation.

14. (Amended) The method of claim 6 wherein said [allele] polynucleotide encoding a form of a mismatch repair protein comprises a truncation mutation.

15. (Amended) The method of claim 7 wherein said [allele] polynucleotide encoding a form of a mismatch repair protein comprises a truncation mutation.

16. (Amended) The method of claim 4 wherein said [allele] polynucleotide encoding a form of a mismatch repair protein comprises a truncation mutation at codon 134.

17. (Amended) The method of claim 6 wherein said [allele] polynucleotide encoding a form of a mismatch repair protein comprises a truncation mutation at codon 134.

18. (Amended) A homogeneous composition of cultured, hypermutable[,] bacteria which comprise a [dominant negative allele] polynucleotide encoding a form of a mismatch repair [gene] protein under the control of an inducible transcription regulatory sequence, wherein said polynucleotide exerts a dominant negative effect when expressed in said bacteria.

26. (Twice Amended) The homogeneous composition of claim 20 wherein [thebacteria comprise] the bacteria express a protein which consists of the first 133 amino acids of PMS2.

31. (Amended) The homogeneous composition of claim 23 comprising a protein which consists of a [eucaryotic] eukaryotic MutS protein.

71. (Amended) The method of claim [26] 3 wherein the dominant negative allele comprises a truncation mutation at codon 134.

In the Specification

Please substitute the following paragraphs, headings, or tables for those in the specification:

At page 18, substitute the following paragraph:

The use of over expressing foreign mismatch repair genes from human and yeast such as PMS1, MSH2, MLH1, MLH3, etc. have been previously demonstrated to produce a dominant negative mutator phenotype in bacterial hosts (35, 36, 37). In addition, the use of bacterial strains expressing prokaryotic dominant negative MMR genes as well as hosts that have genomic defects in endogenous MMR proteins have also been previously shown to result in a dominant negative mutator phenotype (29,32). However, the findings disclosed here teach the use of MMR genes, including the human PMSR2 and PMSR3 gene (ref 19), the related PMS134 truncated MMR gene (ref 32), the plant mismatch repair genes [**(SARAH include Plant patent application)**]and those genes that are homologous to the 134 N-terminal amino acids of the PMS2 gene which include the MutL family of MMR proteins and including the PMSR and PMS2L homologs desribed by Hori et.al. (accession number NM_005394 and NM_005395) and Nicolaides (reference 19) to create hypermutable microbes. In addition, this application teaches the use of DNA mutagens in combination with MMR defective microbial hosts to enhance the hypermutable production of genetic alterations. This accentuates MMR activity for generation of microorganisms with commercially relevant output traits such as but not limited to recombinant protein production strains, biotransformation, and bioremediation.

At pages 19-20, substitute the following paragraph:

Bacterial expression constructs were prepared to determine if the human PMS2 related gene (hPMSR3) (19) and the human PMS134 gene (32) are capable of inactivating the bacterial MMR activity and thereby increase the overall frequency of genomic hypermutation, a consequence of which is the generation of variant sib cells with novel output traits following host selection. Moreover, the use of regulatable expression vectors will allow for suppression of dominant negative MMR alleles and restoration of the MMR pathway and genetic stability in hosts cells (43). For these studies, a plasmid encoding the hPMS134 cDNA was altered by polymerase chain reaction (PCR). The 5' oligonucleotide has the following structure: 5'-ACG CAT ATG GAG CGA GCT GAG AGC TCG AGT-3' (SEQ ID NO: 1) that includes the NdeI restriction site CAT ATG. The 3'-oligonucleotide has the following structure: 5'-GAA TTC TTA TCA CGT AGA ATC GAG ACC GAG GAG AGG GTT AGG GAT AGG CTT ACC AGT TCC AAC CTT CGC CGA TGC-3' (SEQ ID NO: 2) that includes an EcoRI site GAA TTC and the 14 amino acid epitope for the V5 antibody. The oligonucleotides were used for PCR under standard conditions that included 25 cycles of PCR (95^{0}C for 1 minute, 55^{0}C for 1 minute, 72^{0}C for 1.5 minutes for 25 cycles followed by 3 minutes at 72^{0}C). The PCR fragment was purified by gel electrophoresis and cloned into pTA2.1 (InVitrogen) by standard cloning methods (Sambrook et al., Molecular Cloning: A Laboratory Manual, Third Edition, 2001), creating the plasmid pTA2.1-hPMS134. pTA2.1-hPMS134 was digested with the restriction enzyme EcoRI to release the insert (there are two EcoRI restriction sites in the multiple cloning site of pTA2.1 that flank the insert) and the fragment filled in with Klenow fragment and dNTPs. Next, the fragment was gel purified, then digested with NdeI and inserted in pT7-Ea that had been digested with

NdeI and BamHI (filled with Klenow) and phosphatase treated. The new plasmid was designated pT7-Ea-hPMS134. The following strategy, similar to that described above to clone human PMS134, was used to construct an expression vector for the human related gene PMSR3. First, the hPMSR3 fragment was amplified by PCR to introduce two restriction sites, an NdeI restriction site at the 5'- end and an Eco RI site at the 3'-end of the fragment. The 5'-oligonucleotide that was used for PCR has the following structure: 5'-ACG CAT ATG TGT CCT TGG CGG CCT AGA-3' (SEQ ID NO: 3) that includes the NdeI restriction site CAT ATG. The 3'-oligonucleotide used for PCR has the following structure: 5'-GAA TTC TTA TTA CGT AGA ATC GAG ACC GAG GAG AGG GTT AGG GAT AGG CTT ACC CAT GTG TGA TGT TTC AGA GCT-3' (SEQ ID NO: 4) that includes an EcoRI site GAA TTC and the V5 epitope to allow for antibody detection. The plasmid that contained human PMSR3 in pBluescript SK (19) was used as the PCR target with the hPMS2-specific oligonucleotides above. Following 25 cycles of PCR (95^{0}C for 1 minute, 55^{0}C for 1 minute, 72^{0}C for 1.5 minutes for 25 cycles followed by 3 minutes at 72^{0}C). The PCR fragment was purified by gel electrophoresis and cloned into pTA2.1 (InVitrogen) by standard cloning methods (Sambrook et al., Molecular Cloning: A Laboratory Manual, Third Edition, 2001), creating the plasmid pTA2.1-hR3. pTA2.1-hR3 was next digested with the restriction enzyme EcoRI to release the insert (there are two EcoRI restriction sites in the multiple cloning site of pTA2.1 that flank the insert) and the fragment filled in with Klenow fragment and dNTPs. Then, the fragment was gel purified, then digested with NdeI and inserted in pT7-Ea that had been digested with NdeI and BamHI (filled with Klenow) and phosphatase treated. The new plasmid was designated pT7-Ea-hR3.

At page 25, substitute the following table, with different column widths:

STRAIN	# CELLS SEEDED	AMP^R colonies	KAN^R colonies	FREQUENCY
DH10B VEC	50,000	62,000	0	0
DH10B PMS134	50,000	43,146	23	5.3×10^{-4}
BL21 VEC	500,000	520,800	0	0
BL21 T7-Ea-PMS134V5	500,000	450,000	2,245	4.9×10^{-3}
BL21 T7-Ea-PMSR3V5	500,000	500,000	1,535	3.1×10^{-3}

At page 25-26, substitute the following paragraph:

Using the same protocol as listed above and the same cloning strategy, a truncated PMS2 homolog from the *Arabidopsis thaliana* plant, **[(reference the PLANT patent)]**which was cloned by degenerate PCR from an *Arabidopsis thaliana* cDNA library (Strategene), was found to give a similar enhancement of genetic hypermutability in DH5alpha bacteria Figure 5. For detection purposes, we fused a FLAG epitope to the C-terminus of the PMS134 polypeptide using PCR and an antisense primer directed to the 134 codon region of the *Arabidopsis* PMS2 homolog followed by a FLAG epitope and 2 termination codons. The resultant fusion was termed ATPMS134-flag. The AT PMS134-flag gene was then cloned into the IPTG-inducible TACLAC expression vector and transfected into DH5alpha cells. Western blot of bacteria transfected with an IPTG-inducible expression vector carrying a truncated version (codons 1-134) of the Arabidopsis thaliana PMS2 homolog using the anti-FLAG antibody demonstrated the inducibility and steady-state protein levels of the chimeric gene. Figure 5A shows the western blot containing protein from an untransfected cell (lane 1) and a bacterial clone

expressing the Arabidopsis PMS2-134 truncated protein (lane 2). Following the mutagenesis protocol described above, bacterial cells expressing the ATPMS134 protein were found to have an increase in the number of KAN resistant cells (12 clones) in contrast to cells expressing the empty vector that yielded no KAN resistant clone.

At page 37, substitute the following two headings:

Yeast MLH1 cDNA (accession number U07187) (SEQ ID NO: 5)

Yeast MLH1 protein (accession number U07187) (SEQ ID NO: 15)

At page 38, substitute the following two headings:

Mouse PMS2 protein (SEQ ID NO: 16)

Mouse PMS2 cDNA (SEQ ID NO: 6)

At page 39, substitute the following heading:

human PMS2 protein (SEQ ID NO: 17)

At page 40, substitute the following headings

Human PMS2 cDNA (SEQ ID NO: 7)

At page 41, substitute the following two headings:

human PMS1 protein (SEQ ID NO: 18)

932

Human PMS1 cDNA (SEQ ID NO: 8)

At page 42, substitute the following heading:

human MSH2 protein (SEQ ID NO: 19)

At page 43, substitute the following heading:

Human MSH2 cDNA (SEQ ID NO: 9)

At page 44, substitute the following two headings:

human MLH1 protein (SEQ ID NO: 20)

Human MLH1 cDNA (SEQ ID NO: 10)

At page 45, substitute the following three headings:

hPMS2-134 protein (SEQ ID NO: 21)

hPMS2-134 cDNA (SEQ ID NO: 11)

hMSH6 (human cDNA) ACCESSION U28946 (SEQ ID NO: 22)

At page 46, substitute the following three headings:

hPMSR2 (human cDNA) ACCESSION U38964 (SEQ ID NO: 12)

hPMSR2 (human protein) ACCESSION U38964 (SEQ ID NO: 23)

HPMSR3 (human cDNA) ACCESSION U38979 (SEQ ID NO: 13)

At page 47, substitute the following three headings:

hPMSR3 (human protein) ACCESSION U38979 (SEQ ID NO: 24)

hPMSL9 (human cDNA) ACCESSION NM_005395 (SEQ ID NO: 14)

hPMSL9 (human protein) ACCESSION NM_005395 (SEQ ID NO: 25)